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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,653	02/09/2001	Pankaj Qasba	640100-407	7921

7590 07/02/2003

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EXAMINER

WOITACH, JOSEPH T

ART UNIT

PAPER NUMBER

1632

DATE MAILED: 07/02/2003

JP

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.
09/780,653

Applicant(s)

Thiede et al.

Examiner

Joseph Woitech

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Mar 28, 2003

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-8 is/are pending in the application.

4a) Of the above, claim(s) 1-3 and 6-8 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 4 and 5 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on Feb 9, 2001 is/are a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

- Certified copies of the priority documents have been received.
- Certified copies of the priority documents have been received in Application No. _____.
- Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) Other: _____

Art Unit: 1632

DETAILED ACTION

This application is a continuation of 09/316,797, filed May 21, 1999, which claims benefit to 60/086,420, filed May 22, 1998 and 60/108,308, filed November 13, 1998.

Election/Restriction

Applicant's election of group II, claims 4 and 5, in Paper No. 3, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-8 are pending. Claims 1-3, 6-8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was treated as an election without traverse in Paper No. 3. Claims 4 and 5, drawn to a method of treating a patient in need of megakaryocytes comprising administering human mesenchymal stem cells to a patient or administering human mesenchymal stem cells and CD34+ cells to a patient are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Art Unit: 1632

Information Disclosure Statement

It is noted that the specification has provided citations to references throughout the specification, however the cited references have not been provided or made of record. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a subject in need of megakaryocytes as platelet precursor cells comprising administering to said subject autologous or allogenic bone marrow in an amount effective to produce megakaryocytes, does not reasonably provide enablement for administering only mesenchymal stem cells or mesenchymal stem cells and CD34+ cells alone.

Art Unit: 1632

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

State of the prior art. At the time of the invention was made, successful transplantation of hematopoietic progenitor cells had been achieved by expanding CD34+ cells *ex vivo* and engrafting them back into the animal (Berenson *et al.*, page 951; abstract). The engrafted cells were capable producing platelets (*ibid*, page 954; figure 2), indicating that the CD34+ cells

Art Unit: 1632

underwent megakaryocytopoiesis. Importantly, Berenson *et al.* teach that when autologous bone marrow cells depleted of CD34+ cell were transplanted back into an irradiated subject survival and treatment of the subject were greatly reduced over controls (page 952, methods and materials second column and page 954, bridging first and second column). Bertolini *et al.* demonstrated that 'megakaryocytic progenitors' could be generated *ex vivo* and safely administered to a patient (page 2679; abstract). These cells allowed for the recovery of platelet production in patients indicating that the administered cells underwent megakaryocytopoiesis (page 2687; figure 9). However, the method to specifically produce megakaryocytes *in vivo* by administering mesenchymal cells, a supporting cell type which can promote differentiation of CD34+ cells *in vitro*, had not been demonstrated. Moreover, patients lacking a source of CD34+ hematopoietic stem cells clearly have no source of cells capable of differentiating into megakaryocytes.

Nature of the invention and Breadth of claims. The claims are drawn to methods of treatment of a patient in need of megakaryocytes. The claims are broad encompassing treating any subject in need of megakaryocyte cells, however the only specific patients in need thereof taught by the specification are subjects in need of platelet cells and thus, megakaryocytes as the platelet precursor cell. Furthermore, the specification is silent with respect to any disease or condition in which only megakaryocytes are required, and provides only a general guidance to potential subjects as 'individuals receiving chemotherapy, a bone marrow transplant or a peripheral blood stem cell transplant' (page 8, lines 11-12). In each of these circumstances, the individuals require more than only megakaryocytes. The reasons and/or circumstances of 'a

Art Unit: 1632

patient in need of megakaryocytes' alone are not specifically discussed or defined in the specification or the art of record, which has bearing on the predictability of treating a patient in need thereof, because the effective amount to be administered can not be clearly assessed lacking any specific condition or disease to be treated.

The claimed methods comprises administering mesenchymal stem cells and relies on the ability to promote megakaryocyte differentiation of CD34+ cells (present in claim 5). CD34+ hematopoietic stem cells are the cells in the bone marrow capable of differentiating and giving rise to multiple lineages including megakaryocytes. However, with regard to the individuals contemplated for treatment specifically taught in the specification ('individuals receiving chemotherapy, a bone marrow transplant or a peripheral blood stem cell transplant' (page 8, lines 11-12)), none of these subjects contain the CD34+ hematopoietic stem cells which are capable of being induced and differentiating into megakaryocytes. Accordingly, claim 4 encompasses providing mesenchymal stem cells to a subject under conditions wherein the cells to be affected, the CD34+ cells, are not present.

Additionally, the claims are broad encompassing the delivery of any type mesenchymal stem cell. The applicant describes preferable source as the bone marrow (page 6; line 12), however, a mesenchymal cell is defined as relating to a cell type arising from a mesenchyme origin (Stedman's; p. 1093) thus, encompasses a stem cell derived from various mesenchymal derived tissues. However, as known in the art and as summarized by Dexter *et al.* 'cells from the spleen, liver, or other tissues do not support hemopoiesis *in vitro*' (page 432, first column).

Art Unit: 1632

Furthermore, the claims are not limited to administering autologous or allogenic mesenchymal stem cells, and broadly encompass xenogeneic cell transplantation which to date has not been successfully performed for any form of treatment. The specification specifically contemplates using non-matched donor cells (page 6, lines 4-6), and therefore encompasses transplantation of cells to a subject from an unrelated species. In both cases the specification is silent with respect to any discussion or guidance to overcome these long time art recognized limitations

Working Examples and Guidance in the specification. There is no working example nor guidance regarding the method of administration of mesenchymal cells on megakaryocytopoiesis *in vivo*. The specification demonstrates that mesenchymal cells can affect CD34+ cells *in vitro*, however, only refers generally to use of production of differentiated megakaryocytes (page 11, line 15), and does not disclose any guidance regarding administration or conditions to produce these affects *in vivo*. The prior art supports the specification in that the effect of mesenchymal cells *in vitro* is a reproducible phenomenon, however, the specification does not disclose an expected outcome of treatment, nor effective amounts of cells that would produce the expected outcome *in vivo*. Generally, Emerson points out the benefits of cellular therapeutics and the initial clinical success of transplanting multi potent hematopoietic cells (page 3082; third paragraph), and so while it may be possible to reproduce *in vitro* effects *in vivo*, certain *in vivo* conditions must be present. Specifically with respect to claim 4, applicant assumes that hematopoietic cells are present in the patient which could differentiate into megakaryocytes. However, as summarized above, Berenson *et al.* teach that when autologous bone marrow cells

Art Unit: 1632

are depleted of CD34+ cell are transplanted back into an irradiated subject survival and treatment of the subject were greatly reduced over controls (page 954, bridging first and second column).

With respect to claim 5, the present invention relies on the extension of the experiments done *in vitro* and the ability of mesenchymal cells to provide the factors necessary to differentiate hematopoietic stem cells into megakaryocytes, however the absolute need of mesenchymal cells *in vivo* is suspect since it has already been demonstrated *in vivo* that administration of CD34+ cells alone are enough to produce megakaryocytes (Srour *et al.* p. 3336, table 1) and platelet formation (Berenson *et al.* p.953, table I).

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2146.03). The applicants have not demonstrated, or disclosed prior art demonstrating that differentiation effects of isolated mesenchymal cells can occur *in vivo* when administered to a patient. With respect to claim 4 applicant makes the supposition that a stem cell capable of producing a megakaryocyte is present *in vivo*, and with respect to claim 5, that administration of both mesenchymal supporting and stem cell would allow for megakaryocytopoiesis. Beyond the ability of CD34+ cells alone to recover megakaryocytopoiesis (discussed *supra*), or providing mesenchymal stem cells and CD34+ hematopoietic stem cells in the context of a bone marrow transplant, it is uncertain that a treatment encompassed by the method of these claims is possible. Emerson reviews the success of expanded bone marrow cultures ability to recover megakaryocytopoiesis in patients (page 3085; section on INITIAL CLINICAL EXPERIENCE...), and described the successful

Art Unit: 1632

engraftment of *ex vivo* expanded CD34+ cells (last paragraph). However, all the methods described to restore megakaryocytopoiesis *in vivo* have relied on administration of a “stem cell” or “progenitor cell” which is capable of differentiating into the desired cell type, and to date, there is no report that administration of a “mesenchymal cell” would produce the same effect as a “stem cell” upon administration.

In addition, beyond the general teaching of the specification for deficiencies of megakaryocytes in a subject, the art teaches that the presence of low amounts of megakaryocytes can be due to physiological conditions as is found in thrombocytopenia, megaloblastic anemia, or in a patient who is deficient in folate or Cbl where maturation of megakaryocytes can be disrupted (Handin *et al.*, pages 1399-1401). In these instances, the lack of megakaryocytes is due to an inhibition of differentiation of CD34+ hematopoietic stem cells. Therfore, a method of treatment as stated in claims 4-5 would not produce megakaryocytes in such a patient in need of megakaryocytes because the claimed method does not remedy nor address the fundamental physiological problem in these types of subjects.

35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), and that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman*, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Furthermore, the courts have held that in applications directed to inventions in arts where the

Art Unit: 1632

results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In the instant case there is no disclosure of even one working example *in vivo*. As discussed above, subjects contemplated by the specification as needing megakaryocytes are patients in which most or all of the hematopoietic system has been impaired or destroyed. Therefore, these patients lack hematopoietic stem cells which are capable of differentiating into megakaryocytes. In these patients administering mesenchymal stem cells will have no affect on megakaryocyte formation because the required cell types mesenchymal stem cells could potentially affect are not even present. The specification is silent to discussion of any other conditions requiring megakaryocytes, and in view of the art, the physiologically basis of these disorders would indicate that the claimed methods would not remedy their fundamental deficiencies.

Amount of experimentation necessary. The prior art demonstrates that megakaryocyte development is a complex, multi-step process dependent on numerous positive and negative affecters as well as specific cell-cell interaction (page 1, summary of thromboiesis by Ellis *et al.*) It is noted that differentiation of progenitor cells into megakaryocytes *in vitro* has been achieved using various culturing conditions and addition of growth/stimulating factors to the media, and that explant of bone marrow, in particular the CD34+ hematopoietic stem cells in the marrow are capable of differentiating into megakaryocytes *in vivo*. Applicants have defined a potential use of an *in vivo* method of treatment using mesenchymal cells, but essentially have left all of the work required to develop a working method *in vivo* for any patient in need of megakaryocytes

Art Unit: 1632

has been left to others. The specification fails to provide the necessary guidance to overcome art recognized limitations encompassed by the breadth of the claims and fails to provide a nexus from observations made in an *in vitro* culture system to an *in vivo* method of treatment of a patient.

In view of the lack of guidance, working examples, breadth of the claims, skill in the art and state of the art at the time of the claimed invention, it would require undue experimentation by one of skill to practice the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Lemoli *et al.*

(Acta Haematologica 95:164-170, (1996)) as evidenced in Developmental Biology (page 357).

The claims are directed to providing megakaryocytes to a patient in need thereof. The specification is silent with respect to any specific condition wherein only megakaryocytes are required, but teaches generally that a subject in need of platelets, such as individuals receiving chemotherapy or bone marrow transplant, would benefit from the instantly claimed

method (page 8, lines 8-12). With respect to the single method step recited in the claims, the administration of mesenchymal stem cells (claim 4) and the administration of mesenchymal stem cells and CD34+ cells is broad encompassing any means of delivery and the delivery of the cells in any composition. The specification contemplates any process of obtaining mesenchymal stem cells or co-recovery of hematopoietic progenitor cells and mesenchymal stem cells (page 6, lines 18-24) which could subsequently be used in the claimed methods. The specification teaches that a preferred source of mesenchymal stem cells is the bone marrow (page 6, lines 11-12). Accordingly, a reasonable interpretation of the instant claims in light of the guidance of the instant specification is a method comprising administering bone marrow to a subject who has undergone radiation therapy wherein said therapy ablates the cells of the hematopoietic system.

Lemoli *et al.* teach a method of autologous bone marrow transplantation to patients undergoing myeloablative chemotherapy (page 165, Study Design section). Specifically, bone marrow was removed from the patient before chemotherapeutic treatment (page 165, BM samples section). Analysis of the patients after myeloablative treatment and delivery of the autologous bone marrow indicated that an increase in platelets could be detected (summarized in figure 2, lower graph). Lemoli *et al.* does not specifically characterize or state that megakaryocytes are produced by this procedure, however the formation of platelets, the end product of megakaryocyte differentiation, is a clear indication that megakaryocytes are formed in the subject (see figure 9.39 on page 357 in Developmental Biology as evidence of megakaryocyte

Art Unit: 1632

differentiation pathway). Thus, the development of platelets indicates that sufficient amounts cells were administered to affect the patient.

The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See *Ex parte Phillips*, 28 USPQ 1302, 1303 (BPAI 1993) and *Ex parte Gray*, 10 USPQ2d 1922, 1923 (BPAI 1989). In this case, in light of the teaching and guidance of the specification the limitations of an autologous bone marrow transplant to patients who have undergone chemotherapeutic treatment, and the evidence of recovery of platelet formation in said patients after the administration of bone marrow anticipates the instantly claimed methods.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

US Patent 6,225,119, by the same inventors of the present application, is drawn to methods of co-culturing hematopoietic stem cells and mesenchymal stem cells to produce megakaryocytes *in vitro*.

Villeval *et al.* Blood, 90(11):4369-4383, (1997).

Art Unit: 1632

Molineux *et al.* Stem Cells 15:43-49, (1997).

Molinieux *et al.* Blood 88(4)1509-1514, (1996).

Each of the above references provide additional evidence that at the time of filing bone marrow transplants were performed to restore the hemoatopoietic system in an animal. Beyond providing only bone marrow, each provide a characterization of the various differentiated cells types which were formed after the bone marrow transplant, and a further characterization of the affects of co-administering various growth/stimulating factors believed to influence differentiation of a hematopoietic stem cells *in vitro*.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers

Art Unit: 1632

must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703)308-4242 and (703)305-3014.

Joseph T. Woitach

Joe Woitach
AV1632